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EXAMINER

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ATTACHMENT TO ADVISORY ACTION

8. CONT. Applicant has submitted along with their response three references as evidence which have not been considered as no explanation as to why this evidence is necessary and why it was not submitted earlier as required by 37 CFR 1.116(e) has been provided.

11. CONT. The rejection of claim 24 under 35 U.S.C. 103(a) as being unpatentable over Gurunathan et al. (1997) J. Exp. Med., Vol. 186(7), 1137-1147, in view of U.S. Patent No. 6,451,593 (2002), hereafter referred to as Wittig et al., and Makkerh et al. (1996) Current Biology, Vol. 6 (8), 1025-1027, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that Gurunathan et al. teaches the importance of IL-12 and IFN-gamma in generating effective immune responses to the LACK antigen and that Gurunathan et al. suggests that immunostimulatory bacterial sequences present in the plasmid encoding LACK may contribute to the generation of IL-12 and IFN-gamma. Applicant continues by arguing that since Gurunathan et al. teaches the contribution of bacterial sequences present in the plasmid that the skilled artisan would not have been motivated to use a MIDGE vector which lacks the majority of these sequences to express p36 LACK. In response, it is first noted that the sole claim under examination is a product claim, not a method claim. While the product is identified as a "vaccine for vaccinating a living being against infection by leishmania", the patentability of the product depends on the claimed structure of the product and not on its intended use as a vaccine for vaccinating. However, it is also noted that while Gurunathan et al. comments that bacterial immunostimulatory sequence present in the plasmid may contribute to the observed immune response to LACK, the actual data presented by Gurunathan et al. shows that whereas the control plasmid, which theoretically contains the immunostimulatory sequences, does not appear to induce any detectable amount of IFN-gamma when administered *in vivo*, the plasmid encoding LACK DNA induced significant amounts of IFN-gamma (see Figure 7, the control DNA lane, and Figure 5). In fact, the control DNA appears to stimulate IL-4 production, not IFN-gamma production in these experiments (see Figure 5B). Since IL-4 is detrimental to the

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induction of therapeutic immune responses in *Leishmania*, the skilled artisan reading Gurunathan et al. could only conclude that it is the LACK DNA itself and not the bacterial DNA that induces IFN-gamma and results in the generation of a therapeutic immune response in vaccinated mice challenged with *L. major*. Furthermore, as noted in the rejection of record, Wittig et al. supplements Gurunathan et al. by teaching that MIDGE constructs encoding antigens are capable of generating therapeutic immune responses and have several advantages over complete plasmid vectors which have been discussed in detail in previous office actions. As such, the skilled artisan, when reading the teachings of Gurunathan et al. as a whole, in view of Wittig et al. would in fact have been motivated to make a MIDGE construct encoding p36 LACK. In addition, based on the data in Gurunathan et al. discussed above, and the teachings of Wittig et al., the skilled artisan at the time of filing would have had a reasonable expectation that a MIDGE construct encoding p36 LACK could be used as a vaccine.

The applicant further argues that the use of PKKKRKV as the NLS is not obvious from the teachings of Wittig et al. because Wittig et al. discloses the use of three different signal peptides, one of which is the SV40 NLS, and according to applicant there would have been uncertainty as to which of the three would be successful when covalently attached to a MIDGE construct in nuclear localization. The applicant also states that Wittig et al. does not specifically teach SEQ ID NO:3 and that it is irrelevant that this sequence was already known, as taught by Makkerh, because the crucial selective step is to decide which of the three variants proposed by Wittig would be successful. In response, since the SV40 NLS RKKKRKV was well known as a nuclear localization signal sequence and Wittig et al. clearly teaches that covalent attachment of an NLS such as the SV40 NLS to a MIDGE construct, there is clear motivation to make such a construct. As applicant concedes in their remarks, the NLS of SV40, and specifically SEQ ID NO:3, was well known at the time of filing, and had been used successfully in the prior art for nuclear localization. There is no evidence of record to suggest that the skilled artisan would have considered it unpredictable to use any known NLS covalently attached to a MIDGE as taught by Wittig et al. for nuclear localization, or that the skilled artisan would have considered it unpredictable that the well known SV40 NLS would be functional for nuclear localization when covalently attached to a MIDGE. As such, applicant's argument is not found persuasive.

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The applicant then argues that the Declaration previously provided with the response of 5/9/08 does provide evidence of unexpected results. According to applicant, the functional unit of the NLS sequence used in Lopez-Fuertes et al. is the same as SEQ ID NO:3 and the additional short amino acid sequence EDPYC added to PKKKRKV was known in the prior art and is nonfunctional. The applicant also argues that the wording of claim 24 does not limit the present invention to only PKKKRKV. In response, it is first noted that claim language of claim 24 clearly recites "...at least one oligopeptide consisting of the amino acid sequence of SEQ ID 3". The language "consisting of" is not open language. It has been well established in case law to be closed language such that the use of the phrase "consisting of" does not allow for the presence of additional amino acids other than SEQ ID NO 3 in the oligopeptide. As such, applicant's argument that the claim language allows for additional amino acids is not persuasive. As to the argument that the extra amino acids are nonfunctional, there is no evidence of record to suggest that the longer oligopeptide in Lopes-Fuertes et al. is identical in function to the smaller PKKKRKV sequence. Thus, it is not agreed that the evidence provided in Lopez-Fuertes et al. is commensurate in scope to the instant claim.

Finally, the applicant argues Lopez-Fuertes et al. demonstrates unexpected results by showing that prime and boost with MIDGE-p36-NLS generates comparable immune responses as priming with pMOK-p36 and boosting with rVVp36. The applicant also states that the examiners statements regarding greater effects and unexpectedness or expectedness are confusing. In response, it is first noted that the examiner cited *Ex parte The NutraSweet Co.* because applicant's previous response stated that priming and boosting with NLS-modified MIDGE encoding p36 was superior to the best vaccination protocols available. In response, the examiner provided an analysis of the data in Lopez-Fuertes et al. which shows that in fact prime/boost with MIDGE-p36-NLS was comparable to, not superior to, prime/boost with pMOK-p36/rVVp36. The applicant now argues that this comparable response still represents unexpected results because the generation of protective immunity is a complex process such that success with a plasmid vector encoding p36 would not be predictive of success with MIDGE-p36-NLS. In response, this is not agreed for reasons of record. First, the claim is a product claim, not a method of generating protective immunity. Second, as discussed in detail above, Wittig et al. teaches that MIDGE constructs encoding antigens are capable of generating therapeutic

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immune responses and have several advantages over complete plasmid vectors. Also, as discussed above, the actual data presented by Gurunathan et al. shows that the control plasmid, presumably comprising immunostimulatory sequence, induced IL-4 not IFN-gamma, whereas the plasmid encoding LACK DNA induced significant amounts of IFN-gamma, such that the skilled artisan reading Gurunathan et al. could only conclude that it is the LACK DNA itself or expression product thereof and not the bacterial DNA that induces IFN-gamma and results in the generation of a therapeutic immune responses in vaccinated mice challenged with *L. major*. It is also noted that the state of the art for generating immune responses against pathogenic antigens at the time of filing included teachings that numerous expression vectors were capable of expressing pathogenic antigens and generating antigen specific immune responses, including plasmids, adenoviral vectors, retroviral vectors, vaccinia virus vectors, herpes virus vectors etc., such that the skilled artisan would indeed have had a reasonable expectation of success that a MIDGE-p36-NLS as taught by the combined teachings of Gurunathan et al. in view of Wittig et al. and Makkerh et al. could be used to generate immune responses *in vivo*.

Please note that applicant's statements regarding the teaching of two Kalderon et al. publications and a publication by Zanta et al. submitted with the after-final response have not been considered since the applicant has not explained why this evidence is necessary and why it was not submitted earlier as required by 37 CFR 1.116(e).

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

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Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/

Primary Examiner, A.U. 1633